

SPECIFICATION

To All Whom It May Concern:

5

Be It Known That We, Dr. Rajiv Indravadan Modi, Mr. Yatish Kumar Bansal, and Dr. Bakulesh M. Khamar, residents of the city of Gujarat, country of India, whose post office addresses are 13 Sanjeev Baug Society, New Sharda Mandir

10 Road, Ahmedabad 380 007, Gujarat, India; B/5, Kinjal Apartment, Near Parimal Hospital, Maninagar, Ahmedabad 380 008, Gujarat, India; and 201, "Ashadha", Vasundhara Colony, Gulbai Tekra, Ahmedabad 380 006, Gujarat, India, respectively, have invented new and useful improvements in

15 STABLE ORAL PHARMACEUTICAL FORMULATION
CONTAINING AN ANTI-INFECTIVE AGENT AND A MICROORGANISM

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a division of copending application Serial No. 09/045,890 filed March 23, 1998. Priority of Indian application 174/BOM/97 filed March 27, 1997 is claimed under 35 U.S.C. § 119.

5 STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable.

BACKGROUND OF THE INVENTION

- 10 The present invention relates to a process of manufacturing a formulation containing anti-infective agent(s) with viable organisms, which are susceptible to anti-infective agents. Microorganisms are used to prevent adverse effects like diarrhea caused by anti-infective agents.
- 15 The present invention is directed to a formulation wherein anti-infective agents and susceptible viable organisms are combined in such a way that microorganisms, though susceptible to anti-infective agent, remain viable for the shelf life of a formulation and/or until they are consumed. Susceptible organisms are usually combined with anti-infective agents to prevent or minimize adverse effects of anti-infective agents like diarrhea, pseudomembranous colitis, mega colon, etc.
- 20 Organisms are classified as pathogens and commensals. Pathogens are responsible for various infectious diseases and are not normally present in that part of the body. They are also known as infectious agents. Commensals are normally present in various parts of body and perform useful functions. They provide vitamin K, B-12, Thiamine, Riboflavin etc. to the body.¹ They inhibit the growth of pathogens

by a variety of mechanisms.² Anti-infective agents are used to treat or prevent infectious diseases. They kill organisms by various ways. However they are not always specific for pathogens and also kill commensals.²

Destruction or reduction in the number of commensals results in loss of function of commensals and various effects of these are seen.^{2,5} These effects are known as adverse effects or side effects of anti-infective therapy. Diarrhea with or without super-infection is one of such effects seen with anti-infective therapy.^{3,4,6} Diarrhea is seen as an adverse reaction to many antibiotics, but it is most commonly seen with broad-spectrum antibiotics. The incidence of diarrhea also depends on the level of absorption from the G. I. tract. It is less frequent with those getting completely absorbed compared to incompletely absorbed. It also depends on the amount of drug used. The antibiotics causing diarrhea include clindamycin, ampicillin, amoxycillin, cephalosporins (e. g. cefuroxime axetil, cefixime, cepahlexin ceftriaxone), amoxycillin + clauvanic acid, ampicillin + salbcutam, fluoroquinolens and other combinations of broad spectrum antibiotics, e. g. amoxycillin + cloxacillin.

3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 16, 18 Diarrhea can be benign and secondary to transient dysfunction of normal colonic flora due to anti-infective agents⁶ or super-infection by pathogens like clostridium difficile following alteration of normal flora by anti-ineffective agents.^{7, 4, 19, 20} Management in such an event requires cessation of anti-infective therapy^{3, 7, 4} and use of other therapies. Other therapies which can be used include different kinds of anti-infective agents e.g. metronidazole, vancomycin,^{3, 13, 8} teicoplanin and/or use of organisms like lactobacilli, biofidobacterium, saccharomyies boulardili, streptococcus thermophilus, enterococcus facecium SF

- 68, L Casei GG etc.^{14, 15, 16} These can be combined with whole bowel irrigation with good results.¹⁷ The organisms used⁹ eradicate or help in eradicating pathogens by a variety of mechanisms, which include production of hydrogen peroxide or inhibition or adherence of pathogens to intestinal cells. Anti-infective agents-induced diarrhea prolongs treatment and increases the cost of therapy by increased number of ¹drugs to be used, ²days of hospitalization and ³consultations. Sometimes it creates a life threatening situation, e.g. pseudomembranous colitis, ^{4,13, 20} toxic megacolon.
- The organisms named above can be used to treat diarrhea when it occurs. They can also be used to prevent diarrhea.^{14, 16, 18} Commercially available preparations include lactobacillus alone (Lactiflora, Lactobacil, Lactocap, Lactovit, Sporlac) or in combination with streptococcus (Lacticyn) or Sacchromyces (Laviest). To prevent diarrhea, organisms are given along with the anti-infective agents. This requires consumption of a minimum of two different drugs, i.e. an anti-infective agent and an organism. This decreases compliance of a patient.
- Attempts have been made to put organisms and anti-infective agents into one formulation. Some of these are commercially available. Lactobacillus is a commonly used organism. Anti-infective agents used in the formulation include ampicillin, (e. g. Alcillin plus from Alpine), amoxicillin (e. g. Alox plus from Alpine), ampicillin + cloxacillin (e. g. Amplus from Jagsonpal, Elclox plus from Elder, Penmix plus from Dee Pharma, Pen plus from Systopic, Poxin Plus from Alpine), amoxicillin + cloxacillin (e. g. Bicidal plus from Kee Pharma, Diclox from Croford Pharma, Twinclox plus from Alpine). They all are a simple admixture of anti-infective agents and susceptible organisms. However, analysis of commercially available admixtures,

as well as those prepared by us revealed that organisms incorporated into the formulation does not remain viable and did not perform any useful function for which they were to be used. Neither organisms nor their activity could be detected as early as seven days after putting lactobacilli with various antibiotics like ampicillin,

- 5 amoxycillin, amoxycillin + cloxacillin etc. or in a commercially available preparation.

Though 60 million spores are put into formulation, none of them could be grown or demonstrated viable on glucose yeast extract agar plate. It also failed to produce lactic acid as evaluated by consumption of NaOH.

REFERENCES

1. Gastrointestinal tracts chapter 65 in Text Book of Medical Physiology ed. Arther C. Guyton & John E. Hall, Publishers Prism Books (Pvt.) Ltd., 9th edition 1996
2. pp. 1042 anti-microbial agents, chapter 44 in the Pharmacological Basis of Therapeutics in Goodman & Gillman
3. PP-586 antibiotic associated colitis, Chapter 14 in Current Medical Diagnosis & Treatment 36th edition.
4. A. P. Ball, Chapter 7, Toxicity in antibiotic and chemotherapy seventh edition. edit. Francis O'Gerard
5. Betalactam therapy and intestinal flora, Journal of Chemother. 1995 May; 7 suppl 1: 25-31
- 20 6. Diarrhea caused by antibiotic therapy. Rev-Prat. 1996 Jan 15; 46 (2): 171-6
7. Antibiotic associated diarrhea in light of personal observations. Pol-Tyg-Lek. 1995 Sep; 50 (36): 45-9
8. Antibiotic-induced colitis. Semin-Pediatr-Surg. 1995 Nov; (4 (4): 215-20

9. Clostridium difficile acquisition rate and its role in nosocomial diarrhea at a University Hospital in Turkey. Eur-J-Epidemiol. 1996 Aug ; 12 (4): 391-4
10. Risk factors associated with Clostridium difficile diarrhea in hospitalized adult patients: a case-control study---sucralfate ingestion is not a negative risk factor.
- 5 Infect-Control-Hosp-Epidemiol. 1996 Apr ; 17 (4): 232-5
11. Clinical comparison of cefuroxime axetil and amoxycillin/clavulanate in the treatment of patients with secondary bacterial infections of acute bronchitis. Clinical Ther. 1995 Sep-Oct ; 17 (5): 861-74
- 10 12. Clinical comparison of cefuroxime axetil suspension and amoxycillin/lavulanate suspension in the treatment of pediatric patients with acute otitis media with effusion. Clinical Ther. 1995 Sep-Oct: 17 (5): 838-51
13. Antibiotic-associated pseudomembranous colitis: retrospective study of 48 cases diagnosed by colonoscopy. Therapy. 1996 Jan-Feb; 51 (1): 81-6
14. Biotherapeutic agents. A neglected modality for the treatment and prevention of selected intestinal and vaginal infections. JAMA 1996 Mar 20; 275 (11) : 870-6
- 15 15. The pharmacologic principles of medical practice, Krantz & Carr
16. Prevention of beta-lactam-associated diarrhea by saccharomyces boulardii compared with placebo. Am. J. Gastroenterol. 1995 Mar ; 90 (3): 439-48
- 20 17. Whole-bowel irrigation as an adjunct to the treatment of chronic, relapsing Clostridium difficile colitis. J-Clin-Gastroenterol. 1996 Apr ; 22 (3): 186-9
18. Prophylaxis against ampicillin-associated diarrhea with a lactobacillus preparation. Am. J. Hosp. Pharm. 1979 Jun ; 36: 754-757
19. Clostridium difficile in antibiotic associated pediatric diarrhea. Indian Pediatr.

1994 Feb; 31 (2): 121-6

20. Side effects and consequences of frequently used antibiotics in clinical practice.

Schweiz-Med-Wochenschr. 1996 Mar 30; 126 (13): 528-34

BRIEF SUMMARY OF THE INVENTION

5 An object of the present invention is to combine susceptible organisms into a pharmaceutical composition containing anti-infective agents and keep them viable for the shelf life of the formulation or until it is consumed.

A further object of the present invention is to minimize side effects of anti-infective agents resulting from destruction/alteration of normal flora by providing
10 viable organisms along with anti-infective agent(s).

A further object of the present invention is to provide a pharmaceutical composition which is effective after a longer period of storage.

A further object of the present invention is to increase compliance by reduction or elimination in side effects of anti-infective agents.

15 A further object of the present invention is to improve compliance by providing two drugs in one pharmaceutical composition.

A further object of the present invention is to provide an organism at a desired site.

The following specification particularly describes and ascertains the nature of
20 this invention and manner in which it is to be performed.

The susceptible organisms are combined into the formulation in such a way that the organisms remain viable for the shelf life of a formulation in spite of being in contact with the anti-infective agent. To protect susceptible organisms from the

effect of anti-infective agents, a protective barrier is created around the organisms or anti-infective agents, in such a way that the anti-infective agents cannot have an effect on the organisms. This results in viable organisms in the presence of anti-infective agents. The organism remains viable as long as the barrier is maintained.

- 5 This is like applying paint or a film on a substance to prevent corrosion by isolating it from surroundings.

The present invention provides an appropriate barrier by way of a selected coating to one of the active ingredients in such a way that microorganisms are not affected by anti-infective agents. This results in a stable composition. By using an 10 appropriate coating technique, the composition is made to remain stable over a period of 3-36 months at ambient/room temperature. The ratio of a microorganism to anti-infective agents in a composition can be 1:2 to 1:25 by weight. The ratio of 1:5 by weight is found to be optimal for the purpose. The amount of coating is dependent on the type of coating technique, dosage form i.e. capsule, tablet or liquid 15 and desired shelf life. The microorganisms of the composition were found to be active after a variable time period. They also provided a therapeutic effect and eliminated gastro intestinal disturbances associated with anti-infective agents when evaluated in humans.

- The protective barrier is selected depending on the route of administration 20 and the dosage form of the pharmaceutical composition (anti-infective agent + organism).

The pharmaceutical composition so manufactured is evaluated for stability and efficacy.

The pharmaceutical composition so manufactured is evaluated at different test conditions of temperature and humidity (45°C, 37° C at 80% relative humidity and ambient temperature) for time interval extending up to 12 months.

The samples of formulation were taken for study at 3-week intervals. Samples
5 were analyzed for presence of organisms by quantitative and qualitative microbiological techniques. These values were found to be comparable with the amount of organisms introduced into the formulation.

The samples of formulation were also analyzed for presence of anti-infective agent by quantitative estimation. The values of anti-infective agents forms were
10 found to be comparable to those introduced into the formulation.

Thus, findings indicate the presence of organisms and anti-infective agents in the same amount when the formulation was evaluated at different time interval after it was exposed to different environments.

The formulations so created were found to have improved therapeutic efficacy
15 in term of reduction/elimination of antibiotic induced diarrhea.

DETAILED DESCRIPTION OF THE INVENTION

Usually ampicillin causes maximum diarrhea amongst penicillin. The reported incidence is as high as 20% with ampicillins. In 40 patients when ampicillin + lactobacilli were given in a pharmaceutical composition prepared as described in this
20 application, none of them developed diarrhea and everybody could complete the full course of antibiotic therapy. The non-development of diarrhea suggests efficacy of a new pharmaceutical composition prepared according to present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

1. Following are examples of formulations containing various anti-infective agents and susceptible organisms. However, it is not intended that the scope of this invention be limited by these examples.

Example I

5 Ampicillin 250 mgm
Lactobacillus 60 million

Example II

Ampicillin 500 mgm
Lactobacillus 60 million

Example III

Amoxycillin 250 mgm
Lactobacillus 60 million

Example IV

Amoxycillin 500 mgm
Lactobacillus 60 million

10 Example V

Cloxacillin 250 mgm
Lactobacillus 60 million

Example VI

Cloxacillin 500 mgm
Lactobacillus 60 million

Example VII

Ampicillin 250 mgm
Lactobacillus 60 million

Example VIII

Ampicillin 125 mgm
Cloxacillin 125 mgm

15 Cloxacillin 250 mgm

Lactobacillus 30 million

Example IX

Amoxycillin 250 mgm
Cloxacillin 250 mgm

Example X

Amoxycillin 125 mgm
Cloxacillin 125 mgm

20 Lactobacillus 60 million

Lactobacillus 30 million

Example XI

Ampicillin 1000 mgm
Sultamicin 500 mgm

Example XII

Ampicillin 250 mgm
Probenecid 250 mgm

Lactobacillus 60 million

Lactobacillus 60 million

Example XIII

Amoxycillin 250 mgm

Amoxycillin 500 mgm

Clavulanic acid 125 mgm

Probenecid 500 mgm

5 Lactobacillus 60 million

Lactobacillus 60 million

Example XV

Amoxycillin 250 mgm

Amoxycillin 250 mgm

Bromhexine 8 mgm

Carbocisteine 150 mgm

Lactobacillus 60 million

Lactobacillus 60 million

10 Example XVII

Amoxycillin 500 mgm

Amoxycillin 500 mgm

Bromhexine 8 mgm

Carbocisteine 150 mgm

Lactobacillus 60 million

Lactobacillus 60 million

Example XIX

15 Cephalexin 250 mgm

Cephalexin 500 mgm

Lactobacillus 60 million

Lactobacillus 60 million

Example XXI

Cephalexin 250 mgm

Cephalexin 250 mgm

Bromhexine 4 mgm

Probenecid 250 mgm

20 Lactobacillus 60 million

Lactobacillus 60 million

Example XXIII

Cephalexin 500 mgm

Cefuroxime Axetil 125 mgm

Probenecid 500 mgm

Lactobacillus 60 million

Lactobacillus 60 million

Example XXV

Cefuroxime Axetil 250 mgm

Lactobacillus 60 million

5 Example XXVII

Cefixime 200 mgm

Lactobacillus 60 million

Example XXVI

Cefuroxime Axetil 500 mgm

Lactobacillus 60 million

Example XXVIII

Cefixime 400 mgm

Lactobacillus 60 million

In above examples anti-infective agents can be used for any therapeutic purpose, which in a therapeutic dosage causes significant adverse effects, which can be prevented by using an organism. The organism can be any which prevents or minimizes adverse reactions of anti-infective agents when taken at the same time. For prevention of diarrhea, pseudomembranous colitis it can be biofidobacterium, sacchormyces streptococcus thermophilus, enterococcus etc. instead of lactobacillus in above examples in their appropriate dosages.

15 2. Following are examples of providing barrier to organisms for different dosage forms. However, it is not intended that the scope of this invention be limited by these examples.

Example I

Capsules:

20 i) Organisms can be lumped together and formulated into a tablet. The tablet is coated with a barrier film. The film-protected organisms are introduced into the capsule independently. An anti-infective agent is put in the capsule containing organisms protected by a barrier film. It can be vice versa.

ii) Organisms can be granulated. Granules containing organisms are coated with a barrier film. Barrier film coated granules are mixed with anti-infective agent before filling them into capsules.

Example II

5 Tablets:

i) Layered tablets:

Organisms are coated and compressed into layers of a tablet. The other layers of a tablet contains an anti-infective agent.

ii) Tablet containing mixture:

10 Granules of organisms are coated with barrier film and mixed with granulated material of anti-infective agents and compressed into a tablet.

iii) Coated Tablets:

Anti-infective agents are formulated into compressed tablets. They are coated.

During coating stage organisms are introduced into the coating. The coating should

15 be capable of protecting organisms from anti-infective agents. It can be vice versa i.e. anti-infective agent is included in coating.

iv) Composite tablet

A tablet with a hole is produced containing anti-infective agents. The hole of the tablet is filled with organisms. The tablet so obtained may be coated for final

20 finishing. Coating/barrier protection is not so much necessary as it is in a capsule form as long as moisture content is controlled and physical separation is maintained in a same tablet. A formulated tablet can be a dispersible tablet or a simple tablet.

Example III

Liquid formulations:

i) The organisms are coated with a barrier film mixed with other ingredients (dry form) of the formulation including anti-infective agents. The product is reconstituted before use by the addition of an adequate amount of liquid.

5 ii) The organisms are coated with barrier film and suspended in a liquid containing anti-infective agents or vice versa. The barrier film is stable in liquid formulation but disintegrates in the body due to alteration in surrounding, e.g.pH.

3. Following are examples of coating agents, which can be used in making a stable fixed dose of pharmaceutical composition containing anti-infective agent(s) and micro-organisms. However, it is not intended that the scope of this invention be limited by these examples.

Chemical Name

Trade Name

1. Cellulose acetate phthalate

Aquateric

15

CAP

Cellacefate

2. Poly (butyl methacrylate. (2-dimethyl aminoethyl)

Eudragit E 100

methacrylate. methyl methacrylate) 1: 2: 1

Eudragit E 12.5

3. Poly (ethyl acrylate. methyl methacrylate) 2: 1

Eudragit NE 30D

20

(formerly Eudragit 30D)

4. Poly (methacrylic acid, methyl methacrylate) 1: 1

Eudragit L 100

Eudragit L 12.5

Eudragit L 12.5 P

5. Poly (methacrylic acid, ethyl acrylate) 1: 1 Eudragit L 30 D-55

Eudragit L 100-55

6. Poly (methacrylic acid, methyl methacrylate) 1 : 2 Eudragit S 100

Eudragit S 12.5

5 Eudragit S 12.5 P

7. Poly (ethyl acrylate, methyl methacrylate, Eudragit RL 100

trimethylammonioethyl methacrylate chloride) 1: 2: 0.2 Eudragit RL PO

Eudragit RL 30 D

Eudragit RL 12.5

10 8. Poly (ethyl acrylate, methyl methacrylate, Eudragit RS 100

trimethylammonioethyl methacrylate chloride) 1: 2: 0.1 Eudragit RS PO

Eudragit RS 30 D

Eudragit RS 12.5

9. Hydrogenated Castor Oil Castrowax

15 Castrowax MP 70

Castrowax MP 80

Opalwax

Simulsol

10. Cetyl Alcohol Crodacol C70

20 Crodacol C90

Crodacol C95

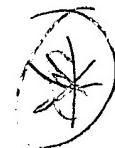
II. Diethyl Phthalate Kodaflex DEP

Palatinol A

| | | |
|-----|--|----------------------------------|
| 12. | Ethyl cellulose | Aquacoat Ethocel Surelease |
| 13. | Hydroxypropyl Cellulose | Klucel |
| 5 | | Methocel |
| | | Nisso HPC |
| 14. | Hydroxypropyl Methylcellulose Phthalate | --- |
| 15. | Zein | --- |
| 4. | Following are examples of methods of preparing fixed doses of stable pharmaceutical compositions. However, it is not intended that the scope of this invention be limited by these examples. | |

another one?

Example I-Double layered Tablet



A stable fixed dose combination layered tablet is prepared using the following components of which the active ingredients are anti-infective agent (s) and micro organisms. The remaining components are physiologically acceptable excipients. One of the active ingredients is coated in a coating pan by the coating process known to those skilled in the art. Excipients are also used along with one of the active ingredients (granules) during tablet making for lubrication as required for the purpose. Granules of separate active ingredients are first prepared by a process known to those skilled in the art. The separate sets of granules are then compressed on a double rotary tablet compression machine having a laying facility at a temperature below 25° C and relative humidity not more than 50% by processes

known to those skilled in the art and the tablets are transferred to a coating pan for film coating to be given by using a film coating process known to those skilled in the art.

i) The relative proportion of anti-infective agents and excipients to prepare

5 coating suspension and coating anti-infective agents before granulation :

| <u>Ingredients</u> | <u>Parts by weight</u> |
|--------------------|------------------------|
|--------------------|------------------------|

| | |
|----------------------|--------|
| Anti infective agent | 77.54% |
|----------------------|--------|

| | |
|-----------------|-------|
| Ethyl cellulose | 2.70% |
|-----------------|-------|

| | |
|-------------------|-------|
| Isopropyl alcohol | 7.42% |
|-------------------|-------|

| | |
|--------------------|--------|
| 10 Dichloromethane | 12.34% |
|--------------------|--------|

ii) The relative proportion of anti-infective agents and excipients to prepare

granules:

| <u>Ingredients</u> | <u>Parts by weight</u> |
|--------------------|------------------------|
|--------------------|------------------------|

| | |
|----------------------|---------|
| Anti-infective agent | 64.08 % |
|----------------------|---------|

| | |
|-------------------------------|--------|
| 15 Microcrystalline cellulose | 26.45% |
|-------------------------------|--------|

| | |
|--------|-------|
| Starch | 9.00% |
|--------|-------|

| | |
|--------------------------|-------|
| Color Sunset Yellow Lake | 0.45% |
|--------------------------|-------|

| | |
|----------------|--------|
| Purified water | 0.02 % |
|----------------|--------|

iii) The relative proportion of excipients to be added to granules containing

20 anti-infective agents as lubricants:

| <u>Ingredients</u> | <u>Parts bv weight</u> |
|--------------------|------------------------|
|--------------------|------------------------|

| | |
|-----------------|--------|
| Sodium chloride | 31.91% |
|-----------------|--------|

| | |
|-----------------|--------|
| Polyplasdone XL | 14.89% |
|-----------------|--------|

| | | |
|---|----------------------------|--------|
| | Microcrystalline cellulose | 21.28% |
| | Saccharine sodium | 10.64% |
| | Flavour orange | 10.64% |
| | Magnesium stearate | 5.32% |
| 5 | Purified Talc | 5.32% |

iv) The relative proportion of microorganisms and excipients to prepare granules:

| <u>Ingredients</u> | <u>Parts by weight</u> |
|--------------------|------------------------|
|--------------------|------------------------|

| | | |
|----|----------------------------|--------|
| | Microorganisms | 18.18% |
| | Starch | 18.18% |
| 10 | Microcrystalline cellulose | 56.67% |
| | Magnesium stearate | 0.91% |
| | Polyplasdone XL | 3.03% |
| | Sodium chloride | 3.03% |

The fixed dose layered tablet compositions, which are prepared through making use of the above described process contains the above active ingredients anti-infective agents and viable organisms in their respective therapeutic concentration. The compositions provide pharmacological effects which are complementary to the effects produced by (Prior art) each individual ingredient and are stable for a period of at least 3-36 months at ambient room temperature.

20 **Example II-Capsules**

Stable fixed dose combination capsules are prepared using following components of which the active ingredients are anti-infective agents and microorganisms. The remaining components are physiologically acceptable

excipients. Granules of one of the active ingredients (e. g. microorganisms) are first prepared by a process known to those skilled in the art. The granules so formed are compressed into a tablet-by-tablet compression machine having a laying facility at a temperature below 25°C and relative humidity not more than 50% by a process

- 5 known to those skilled in the art. Tablets are transferred to a coating pan for coating to be given by a coating process known to those skilled in the art.

The remaining active ingredient is mixed with excipients and filled into gelatin capsules by a process known to those skilled in the art. Before sealing of the capsules, the coated tablet containing active ingredients is introduced into the

- 10 capsules by a process known to those skilled in the art.

- i) The relative proportions of anti-infective agents and excipients for filling in capsule:

| | <u>Ingredients</u> | <u>Parts by weight</u> |
|----|-----------------------|------------------------|
| | Anti-infective agent | 91.94% |
| 15 | Pregelatinised starch | 6.24% |
| | Magnesium stearate | 1.44% |
| | Sodium lauryl sulfate | 0.38% |

- ii) The relative proportion of microorganisms and excipients to prepare granules is as follows :

| | <u>Ingredients</u> | <u>Parts by weight</u> |
|----|-----------------------------|------------------------|
| | Microorganism | 42.86% |
| | Micro crystalline cellulose | 53.93% |
| 20 | Magnesium stearate | 1.07% |

Colloidal silicone dioxide 0.71%

Cross carmelloose sodium 1.43%

iii) The relative proportion of excipients to prepare coating suspension for coating of a tablet containing microorganisms to be kept into a capsule:

| | <u>Ingredients</u> | <u>Parts by weight</u> |
|----|--|------------------------|
| 5 | Hydroxy propyl methyl cellulose pthalate | 4.37% |
| | Titanium dioxide | 0.96 % |
| | Purified Talc | 0.19% |
| | Polyethelene glycol | 0.99% |
| 10 | Isopropyl alcohol | 34.95% |
| | Dichloromethane | 58.54% |

The fixed dose capsule compositions, which are prepared through making use of above described process contain the above active ingredients, anti infective agents, and viable organisms in their respective therapeutic concentrations. The 15 compositions provide pharmacological effect, which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3-36 months at ambient room temperature.

Example III-Liquid Suspension

A stable fixed dose combination liquid tablet is prepared using the following 20 components of which the active ingredients are anti-infective agent (s) and microorganisms. One of the active ingredients is granulated after suspending it in a coating suspension to provide granules of 100 micron or less in size by a processes known to those skilled in the art. Granules so prepared are suspended into a liquid

formulation by processes known to those skilled in the art. The other active ingredient is introduced into the suspension by the process known to those skilled in the art in such a way that final concentration of microorganisms is 20% of anti-infective agent(s)

- 5 The relative proportion of anti-infective agents and excipients to prepare coated granules:

| <u>Ingredients</u> | <u>Parts by weight</u> |
|----------------------------|------------------------|
| Anti infective agent | 56.82% |
| Cellulose acetate pthalate | 22.73% |
| 10 Isopropyl alcohol | 6.82% |
| Dichloromethane | 13.63% |

The fixed dose liquid suspension composition, which is prepared through making use of the above described process contains the above active ingredients, anti-infective agents, and viable organisms in their respective therapeutic concentrations. The composition provides pharmacological effects, which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3-36 months at ambient room temperature.

Example IV - Dry Powder composition to make liquid composition after reconstitution.

- 20 A stable fixed dose combination of dry powder for reconstituting the liquid formulation before use is prepared using the following components of which the active ingredients are anti-infective agent(s) and micro organisms. The remaining components are physiologically acceptable excipients.

One of the active ingredients is granulated after suspending it in a coating suspension by a process known to those skilled in the art. The granules so prepared are dried and mixed with a dry powder containing another active ingredient by processes known to those skilled in the art in such a way that microorganisms are

- 5 20% of anti infective agent(s) by weight.

The relative proportion of anti infective agents and the excipients to prepare coated granules is as follows :

| <u>Ingredients</u> | <u>Parts by weight</u> |
|---|------------------------|
| Anti infective agent(s) | 50% |
| 10 Hydroxy propyl methyl cellulose K-15 M (1, 00, 000 cps) | 45% |
| Purified water | 5% |

- 15 The fixed doses of dry powder compositions, which are prepared through making use of the above described process contains the above active ingredients, anti infective agents and viable organisms in their respective therapeutic concentrations. The compositions provide pharmacological effects, which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3-36 months at ambient room temperature.
- 20 The above composition when reconstituted by adding liquid prior to use remains stable at ambient room temperature for 3 to 7 days.

5. Following are examples of therapeutic dosages of various anti-infective agents and microorganisms. However, it is not intended that the scope of this invention be limited by these examples.

A. Anti-infective agents

Anti infective agents can be penicillins e. g. ampicillin, amoxycillin, cloxacillin, cephalosporins e. g. cephalexin, cefadroxyl, cefuroxime axetil, cefixime, beta lactamase inhibition like clavanic acid, macrolide like erythromycin as single ingredient or combination thereof. *and Ciprofloxacin.*

i). Solid dosage forms like capsules or tablet contains anti infective agents

equivalent to 125,250 or 500 mgm of the active component

ii. Liquid dosage forms usually contain anti infective agents equivalent to 125

mgm of active component in 5 ml.

10 B. Microorganisms, which can be used for therapeutic purposes and the dosages

are as under:

1. Lactobacillus Aciophillus 10 to 100 million

2. Lactobacillus Spores 30-60 x 10⁶

3. Lactobacillus Lactis 10-500 million

15 4. Streptococcus thermophilus 10 million

5. Streptococcus lactis 10 million

6. Saccromyces cerevisea 10 million

7. Lactobacilli GG 10¹⁰units